エンドセリンの受容体及び変換酵素レベルでの心不全形成に果たす意義の解明

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エンドセリンの受容体及び変換酵素レベルでの心不全形成に果たす意義の解明

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はしがき

エンドセリン(ET)系は、血管内皮由来の強力な血管収縮物質として発見されたが、その発現は血管のみに留まらす、心筋細胞にても産生され、特に心血管疾患の終末像である心不全重症度に応じて賦活化する。ET は三つのアイソザイムが同定されているが、その中心となる ET-1 は２つの受容体、ET-A 及び ET-B 受容体を介して単に血管トーヌス調節だけでなく、直接心筋細胞に作用し心不全の病態形成に大きく関与している。実際その受容体レベルでの ET 系抑制が心不全ラットの生命予後を改善することが報告され、ET 系の抑制が心不全治療の新たなターゲットになる可能性がある。しかし二つの大きな問題があると考える。第一に、ET-B 受容体が如何なる病態生理作用を有しているかの解明がなされていない。我々は心不全で ET は ET-B 受容体を介して血管拡張作用を発揮すると報告しているが、その抑制は当然血行動態不利益をもたらすはずである。心不全の生命予後が神経体液因子調節によって規定されると言う事実から考えると、ET 受容体を介する ET 作用の阻害に予後改善的な体液因子バランスの調節効果があると考えられる。第二に、慢性心不全下では ET 受容体の internalization の発生や機能的変化が生じると報告され、長期的な受容体拮抗薬投与の有効性に疑問が残る。ET-1 は前駆体の Big-ET-1 から ET 変換酵素によって ET-1 へ変換され産生されることから、長期的な ET 系阻害として、受容体レベルでなく、前駆体の Big-ET から ET-1 への変換過程を阻害する意義を検討する必要がある。よって今回の研究において、神経体液因子の動態を見るのに適した高頻度ペーシングにて作製した心不全イヌを用いて、以下の二つを個体レベルから細胞、分子レベルまで掘り下げて明らかにしようと取り組んだ。

1）選択的 ET-B 受容体拮抗薬の慢性阻害が神経体液因子発現調節に如何なる影響を及ぼすかを、ET-A 受容体拮抗薬のそれと比較検討する。

2）心不全進展における ET 変換酵素活性の慢性阻害効果を ET-A 受容体拮抗薬の慢性投与と比較し、二つのアプローチの違いを明確にする。

研究組織

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平成 12 年度

1. 第 4 回日本心血管内分泌代謝学会総会

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滋賀医科大学　第一内科
和田厚幸　蔦本尚慶　大西正人　林優　筒井崇　木之下正彦

2. 第 4 回日本心不全学会総会

Angiotensin II and endothelin-1 induce cardiac and vascular remodeling in heart failure
First Department of Internal medicine,　Shiga University of Medical Science
Xinwen Wang, Atsuyuki Wada, Masato Ohnishi, Takayoshi Tsutamoto, Kiyoshi Kurokawa, Hisao Yamada, Masahide Sawaki, Masanori Fuji, Takehiro Matsumoto, Masahiko Kinoshita

平成 13 年度

1. 10th International Congress on Cardiovascular Pharmacotherapy

CHRONIC EFFECTS OF AN ENDOTHELIN-CONVERTING ENZYME INHIBITOR ON THE CARDIAC AND HORMONAL FUNCTIONS IN HEART FAILURE; COMPARISON OF THERAPEUTIC EFFECTS WITH THOSE OF AN ACE INHIBITOR
First Department of Internal Medicine, Shiga University of Medical Science, Shiga, Japan
A. Wada, T. Tsutamoto, M. Ohnishi, M. Fujii, T. Matsumoto,
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2. 第 65 回日本循環器学会学術集会

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M. Ohnishi, A. Wada, T. Tsutamoto, M. Fujii, T. Matsumoto, T. Yamamoto, T Takayama,
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4. Seventh International Conference on Endothelin

CHRONIC EFFECTS OF AN ENDOTHELIN-CONVERTING ENZYME INHIBITOR ON THE CARDIORENAL AND HORMONAL FUNCTIONS IN HEART FAILURE
Atsuyuki Wada, Masato Ohnishi, Takayoshi Tsutamoto, Masanori Fujii, Takehiro Matsumoto, Takashi Yamamoto, Xinwen Wang, Tomoyuki Takayama, Masahiko Kinoshita
First Department of Internal Medicine, Shiga University of Medical Science, Shiga, Japan

Endothelin-1 stimulates endogenous nitric oxide synthetase inhibitor, asymmetric dimethylarginine, in experimental heart failure
Masato Ohnishi1, Atsuyuki Wada1, Takayoshi Tsutamoto1, Masanori Fujii1, Takehiro Matsumoto1, Takashi Yamamoto1, Tomoyuki Takayama1, Xinwen Wang2, Masahiko Kinoshita1. 1First Department of Internal Medicine, Shiga University of Medical Science, Otsu,

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Chronic administration of phosphodiesterase type 5 inhibitor suppress renal production of endthelin-1 during progression of heart failure

Takashi Yamamoto, Atsuyuki Wada, Masato Ohnishi, Takayoshi Tsutamoto, Masanori Fujii, Takehiro Matsumoto, Xinwen Wang, Tomoyuki Takayama, #Kiyoshi Kurokawa, Masahiko Kinoshita

The First Department of Internal Medicine and the Department of Anatomy#, Shiga University of Medical Science, Shiga, Japan

5. American Heart Association 74th Scientific Sessions

CHRONIC EFFECTS OF AN ENDOTHELIN-CONVERTING ENZYME INHIBITOR ON THE CARDIAC STRUCTURAL CHANGES AND GENE EXPRESSION IN HEART FAILURE; COMPARISON OF EFFECTS WITH THOSE OF AN ACE INHIBITOR

Atsuyuki Wada, Masato Ohnishi, Masanori Fujii, Takehiro Matsumoto, Takashi Yamamoto, Tomoyuki Takayama, First Department of Internal Medicine, Shiga University of Medical Science, Shiga, Japan

平成 14 年度

1. American Collage of Cardiology Association 51th Annual Scientific Session

Long-term effects of endothelin-converting enzyme inhibition on cardiac structure and gene expression in heart failure; comparison with ACE inhibition

Takashi Yamamoto, Atsuyuki Wada, Masato Ohnishi, Takayoshi Tsutamoto, Masanori Fujii, Takehiro Matsumoto, Tomoyuki Takayama, Masahiko Kinoshita

First Department of Internal Medicine, Shiga University of Medical Science, Shiga, Japan

2. 第 66 回日本循環器学会学術集会

Endothelin influences the cardiac remodeling process by interacting with cardiac angiotensin-II pathways via ACE and chymase in severe heart failure

Atsuyuki Wada, Takayoshi Tsutamoto, Masato Ohnishi, Masanori Fujii, Takehiro Matsumoto, Takashi Yamamoto, Tomoyuki Takayama, Takashi Tsutsui, Keiko Maeda, Masahiko Kinoshita

First Department of Internal Medicine, Shiga University of Medical Science.

Endothelin influences the cardiac remodeling process by interacting with
cardiac angiotensin-II pathways via ACE and chymase in severe heart failure
高山智行,和田厚幸,大西正人,蔦本尚慶,藤井応理,松本武洋,山本孝,前田圭子,林優,筒井崇,
木之下正彦　滋賀医科大学　第一内科

Long-term phosphodiesterase type 5 inhibition ameliorates pulmonary
hypertension caused by heart failure ~ significant contribution of the
natriuretic peptides-cGMP pathway ~
山本孝,和田厚幸,大西正人,蔦本尚慶,前田圭子,藤井応理,筒井崇,松本武
洋,高山智行,木之下正彦　滋賀医科大学　第一内科

Chronic chymase inhibition prevented cardiac fibrosis and improved diastolic
dysfunction in the progression of heart failure.
松本武洋,和田厚幸,大西正人,蔦本尚慶,藤井応理,山本孝,高山智行,前田圭子,林優,筒井崇,
木之下正彦　滋賀医科大学　第一内科

Endogenous bradykinin improves left ventricle diastolic dysfunction under
the chronic treatment of ACE inhibitor in heart failure
藤井応理,和田厚幸,蔦本尚慶,大西正人,松本武洋,山本孝,高山智行,前田圭子,筒井崇,
木之下正彦　滋賀医科大学　第一内科

3. American Heart Association 75th Scientific Sessions

Endothelin inhibition prevents the cardiac remodeling process interacting with cardiac angiotensin-II generating pathway, ACE and chymase, in heart failure
First Department of Internal Medicine Shiga University of Medical Science, Otsu, Japan
Atsuyuki Wada, Takehiro Matsumoto, Masato Ohnishi, Masanori Fujii,
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研究成果

添付した論文にて報告書に代用する。

（別紙様式 12）　　平成 14 年度科学研究費補助金研究成果報告書概要

1. 機関番号 | 1 | 4 | 2 | 0 | 2 |　2. 研究機関名 滋賀医科大学

3. 研究種目名 基盤研究((C)(2)　4. 研究期間 平成 12 年度 ～ 平成 14 年度

5. 課題番号 | 1 | 2 | 6 | 7 | 0 | 6 | 6 | 1 |

6. 研究課題名 エンドセリンの受容体及び変換酵素レベルでの心不全形成に果たす意義の解明

7. 研究代表者

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8.研究分担者（所属機関名は、研究代表者の所属機関と異なる場合のみ記入すること。）

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	ﾌﾘｶﾞﾅ		
	ﾌﾘｶﾞﾅ		
	ﾌﾘｶﾞﾅ		
	ﾌﾘｶﾞﾅ		

9. 研究成果の概要（当該研究期間のまとめ、600 字～800 字。図、ｸﾞﾗﾌ等は記載しないこと）

エンドセリン(ET)-1 はアンジオテンシン II 産生系と同様に ET 変換酵素 (ECE)によって前駆体 Big-ET から ET-1 へ変換され、ET-A 及び ET-B 受容体を介して血管収縮、心筋細胞肥大や線維増生に機能する。

（1）ETA 受容体拮抗薬 FR139317、ETA/B；TAK044、ETB；K8794 を、ヒト拡張型心筋症に相当する高頻度右室ペーシング心不全イヌに投与し、心不全での ET の意義を検討した。ET は ETA 受容体を介して血管抵抗を増加させ、糸球体濾過率、腎血漿流量を低下させ水ナトリウム貯留的に働くが、遠位尿細管での水再吸収には関係しない。しかし ETB 受容体を介しては、血管抵抗を低下させ腎血漿流量の増加させる。さらに遠位尿細管、集合管での水再吸収を低下させ体液排泄的に作用している。しかしレニンーアンギオテンシンーアルドステロン(RAA)分泌を有意に抑制している事が明らかになった。

（2）ECE とアンジオテンシン変換酵素(ACE)両阻害が心筋リモデリングの形成過程に単独阻害よりも有効かは明かにするため、ECE 阻害薬 FR901533 と ACE 阻害薬エナラプリルを慢性併用投与し心筋リモデリングに及ぼす効果を単独群と検討した。ECE/ACE 阻害薬は各単独治療群と比して左室径の拡大を防止し、左室内圧の上昇を抑制した。不全心での SR Ca2+-ATPase mRNA の upregulation に伴い、拡張能の指標である時定数タウの有意な短縮を認めた。線維化の指標である collagen I、III mRNA の発現を低下させ、picrosirius red 染色で定量したコラーゲン蓄積を抑制した。ECE を介した ET-1 産生は心リモデリング形成に重要な役割を演じているが、ECE/ACE 両阻害薬は単に血行動態の改善にとどまらず、Ca ハンドリングの改善、線維化抑制を介して単独阻害に比してより心不全改善効果を有すると考えられた。

※ 成果の公表を見合わせる必要がある場合は、その理由及び差し控え期間等を記入した調書（A4判縦長横書き1枚）を添付すること。

10. キーワード

(1) エンドセリン　(2) 心不全　(3) アンギオテンシン
(4) 変換酵素　(5) 受容体　(6)
(7)　(8)

（裏面に続く）

11.研究発表（印刷中も含む。）

〔雑誌論文〕

著者名	論文標題			
Matsumoto T, Wada A, Tsutamoto T, Ohnishi M, Isono T, Kinoshita M	Chymase Inhibition Prevents Cardiac Fibrosis and Improves Diastolic Dysfunction in the Progression of Heart Failure.			
雑誌名		巻・号	発行年	ページ
Circulation.		107	2003	2555-2558

著者名	論文標題			
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12.研究成果による工業所有権の出願・取得状況

工業所有権の名称	発明者名	権利者名	工業所有権の種類、番号	出願年月日	取得年月日

11.研究発表（印刷中も含む。）

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和田厚幸、蔦本尚慶、大西正人、澤木政英、藤井応理、松本武洋、木之	心不全における体液恒常性維持に果たす心房性ナトリウム利尿ペプチド及びエンドセリンの役割			
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(別紙様式13)

ABSTRACTS OF RESEARCH PROJECT, GRANT-IN-AID FOR SCIENTIFIC RESEARCH (2002)

1. RESEARCH INSTITUTION NUMBER : 14202

2. RESEARCH INSTITUTION : Shiga University of Medical Science

3. CATEGORY : Grant-in-Aid for Scientific Research (C)(2)

4. TERM OF PROJECT (2000 ~ 2002)

5. PROJECT NUMBER : 12670661

6. TITLE OF PROJECT : Role of endothelins through those receptors and converting enzyme in the progression of heart failure

		REGISTERED NUMBER	NAME	INSTITUTION, DEPARTMENT, TITLE OF POSITION
7. HEAD INVESTIGATOR		10273400	Atsuyuki Wada	Shiga University of Medical Science, Medical Department, Assistant Professor
8. INVESTIGATORS	(1)	70273406	Tetsuya Matsumoto	Shiga University of Medical Science, Medical Department, Assistant Professor
	(2)	〃	〃	〃
	(3)	〃	〃	〃
	(4)	〃	〃	〃
	(5)	〃	〃	〃

9. SUMMARY OF RESEARCH RESULTS

1. Endothelin (ET)-1 not only causes potent vasoconstriction but also leads to fluid retention, which are both mediated by ETA and/or ETB receptors. We administered either the selective ETA receptor antagonist FR173657 (FR) or the mixed ETA/ETB receptor antagonist TAK-044 (TAK) to dogs with heart failure (HF) induced by rapid ventricular pacing. FR increased urinary excretion in association with increased renal plasma flow (RPF) and glomerular filtration rate (GFR) with no significant changes in the fractional reabsorption of water distally (FRWD). In contrast, despite increased GFR, TAK did not alter urine volume or RPF with significantly increased FRWD. The incremental magnitude of GFR and RPF induced by FR was significantly larger than that by TAK. These findings indicate that ETB receptor activation may result in diuresis by renal vasodilatation and blunting water reabsorption in the distal tubules and collecting ducts.
2. We administered K-8794, an orally active selective ET-B receptor antagonist, to dogs with HF. Plasma renin activity and aldosterone increased in both control and K8794 groups, however, levels in the K-8794 group were significantly lower than those in the control group. In the K-8794 group, it was quite interesting to note that Na excretion and urine flow rate were higher than in the control group. Although ET-B receptor antagonism possesses some hemodynamic disadvantages, it can successfully prevent body fluid retention through the suppression of the activation of the renin-angiotensin-aldosterone system in dogs with HF.
3. We examined the combination effects of an ET-converting enzyme inhibitor (FR901533) and an ACE inhibitor (enalapril) on changes in hemodynamics, the expression of molecular markers of HF and the histomorphometry compared with those of monotherapy in dogs with HF. Although there were no differences observed in LV ejection fraction, combination therapy of both inhibitors significantly decreased LV filling pressure, shortened the time constant of relaxation and upregulated the expression of sarcoplasmic reticulum Ca2+-ATPase mRNA. The combination also decreased the expression of collagen type III mRNA and cardiac collagen deposits compared with those of monotherapy. Combining these two modes of enzyme inhibition may further improve LV diastolic dysfunction rather than systolic dysfunction, via modification of nitric oxide rele and Ca2+ handling as well as suppression of collagen accumulation in HF.

10. KEY WORDS

(1) endothelin (2) heart failure (3) angiotensin

(4) receptor (5) converting enzyme (6)

(7) (8)

(CONTINUE TO NEXT PAGE)

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